

ORIGINAL**Androgen replacement therapy for cancer-related symptoms in male advanced cancer patients : study protocol for a randomised prospective trial (ARTFORM study)**

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Abstract : Recent studies reveal that hypogonadism with low serum androgen levels is associated with advanced cancer and induction of most cancer-related symptoms. We designed an ARTFORM study to evaluate the efficacy of androgen replacement therapy in male advanced cancer patients. The ARTFORM study is an investigator-initiated, randomised controlled trial comparing intramuscle injection of testosterone enanthate with non-administration in male advanced cancer patients with non-curative locally advanced or metastatic lesions. Serum total and free testosterone levels are measured and patients with low testosterone level are randomised. The primary endpoint is the difference in validated health-related quality of life questionnaires at week 12. Trial registration of the ARTFORM study is assigned to University hospital Medical Information Network, Center identifier UMIN 000010939. *J. Med. Invest.* 64 : 202-204, August, 2017

Keywords : advanced cancer, androgen replacement therapy, health-related quality of life, randomised controlled trial, testosterone

INTRODUCTION

Although anticancer agents are sometimes used to prolong survival in advanced cancer patients with non-curative locally advanced or metastatic lesions, many symptoms induced by the cancer itself or the adverse events of anticancer agents burden patients regardless of the type of cancer. Recent studies revealed that hypogonadism with low serum testosterone levels is associated with advanced cancer and induces many cancer-related symptoms including depression, weight loss, albumin loss, sarcopenia, topical inflammation, deterioration of pain, increase of opioid dose, and cachexia (1-5). Currently, each symptom is individually treated with a specific therapy. However, it is theoretically possible to treat hypogonadism by androgen replacement therapy to solve all problems at once. In the ARTFORM study, we prospectively examine the efficacy of androgen replacement therapy for cancer-related symptoms in male advanced cancer patients.

PATIENTS AND METHODS*Aim*

We aim to evaluate the efficacy of testosterone enanthate in male advanced cancer patients with non-curative locally advanced or metastatic lesions.

Study design

Our ARTFORM study is an investigator-initiated, randomised controlled trial involving a comparison of intramuscle injection of testosterone enanthate with non-administration in male advanced

cancer patients with low possibility of complete recovery. Patients are randomly assigned to testosterone enanthate administration group or non-administration group, as shown in Figure 1.

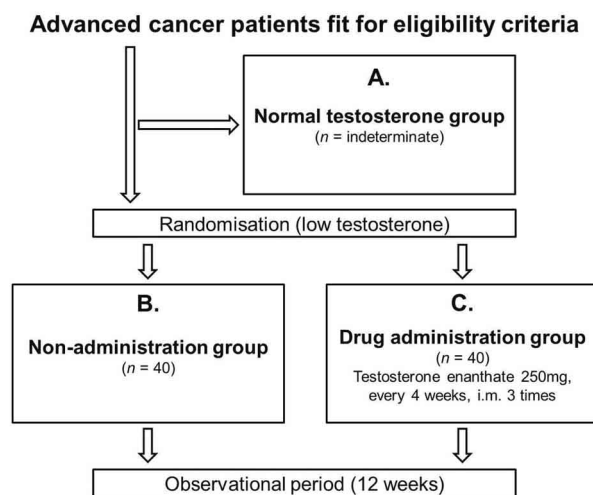


Figure 1. Trial overview

Primary endpoint and additional measures

A validated health-related quality of life questionnaire, FAACT ver4, and the Edmonton Symptom Assessment System (ESAS), translated into Japanese, are administered before the treatment

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and at 4, 8, and 12 weeks after treatment commences to comprehensively evaluate the various aspects of physical and psychosocial well-being.

Eligibility criteria

Inclusion criteria require patients to be male ; have pathologically or cytologically confirmed cancer ; have non-curative locally advanced or metastatic lesions ; know their diagnosis ; provide written informed consent ; and have appropriate hepatic and renal functionality as demonstrated in laboratory tests within 4 weeks prior to registration : aspartate transaminase $\leq 3.0 \times$ upper limit of normal (ULN), alanine transaminase $\leq 3.0 \times$ ULN, blood urea nitrogen ≤ 30 mg/dL, and serum creatinine ≤ 3.0 mg/dL.

Patients are excluded if they are younger than 20 years old ; have prostate cancer, past history of the disease, or severe benign prostate hyperplasia defined as prostate volume > 40 mL with a history of acute urinary retention ; have possible prostate cancer with serum prostate specific antigen level > 4.0 ng/mL ; or are considered by a principal or clinical investigator to be inappropriate for participation in the present study for any other reason.

Informed consent : Ethics approval

The ARTFORM study is conducted in accordance with the Declaration of Helsinki 1975, as revised in 2008. All treatments and examinations for hypogonadism are undertaken following written informed consent prior to registration. The ARTFORM study received approval from the Institutional Review Board of Kanazawa University.

Methods of recruitment and randomisation

Recruitment began in June 2013 and completion is planned by December 2017. Eligible patients have their serum total and free testosterone levels checked and if the total and free testosterone level is ≥ 2.31 ng/mL and 11.8 pg/mL, respectively, patients are assigned to group A and do not proceed to randomisation. If either total or free testosterone level is < 2.31 ng/mL or < 11.8 pg/mL, respectively, patients are randomly assigned to one of two groups : non-administration (group B) or testosterone enanthate administration (group C).

Administration of testosterone enanthate

Testosterone enanthate is injected in muscle of patients who are assigned to the testosterone enanthate group at a dose of 250 mg every 4 weeks. The administration of testosterone enanthate is terminated when any of the following events occur : 1) the patient withdraws written informed consent or opts out of the study ; 2) the patient is no longer eligible for the study ; 3) cancer is completely cured ; 4) the patient's condition deteriorates and testosterone enanthate is not appropriate ; 5) severe adverse events occur ; 6) the patient's compliance is poor ; or 7) the patient's participation is considered inappropriate by a principal or clinical investigator for any other reason.

Data collection

All patients providing written informed consent to participate in the ARTFORM study are asked to provide a complete medical history. Clinical data obtained in the ARTFORM study include the Eastern Cooperative Oncology Group PS, physical measurements (age, height, body weight, body temperature, and blood pressure), haematological measurements (e.g. white blood cell, red blood cell, haemoglobin, haematocrit, and platelet counts), general blood biochemical measurements (e.g. total and free testosterone, alkaline phosphatase, bone alkaline phosphatase, total bilirubin, creatinine, liver enzymes, and electrolytes), cachexia-related biomarkers (IL-6, TNF alpha, IGF-1), urine analysis, and quality of life questionnaires (FAACT ver4 and ESAS). Examinations are per-

formed every 4 weeks for 12 weeks (Figure 2). However, if a principal or clinical investigator considers these examinations to be necessary, they can be performed at any time.

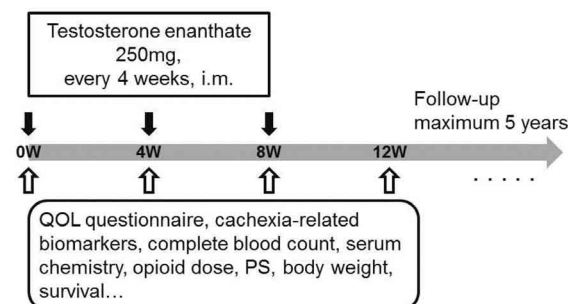


Figure 2. A follow-up schedule

Definition of endpoints

The primary endpoint is the difference in health-related quality of life questionnaires between groups B and C at week 12.

Secondary endpoints are set in the ARTFORM study as follows :

1. Difference in health-related quality of life questionnaires, PS, body weight, body mass index, dose of analgesic, and blood data at registration between normal testosterone group (A) and low testosterone groups (B and C).
2. Difference in PS, body weight, body mass index, dose of analgesic, blood data, cancer-specific survival, and overall survival between groups B and C.

RESULTS

Patient enrolment and anticipated completion of enrolment

Our current expectation is that the final patient will be enrolled by October 2017 and the entire study will be completed by December 2017. Recruitment began in June 2013 and cumulative enrolment reached 70 cases as of February 2017.

DISCUSSION

Recent developments in cancer treatment have prolonged survival of advanced cancer patients, indicating that patients spend a long time not only with cancer but also cancer-related symptoms. Although prolonging life is the main goal of cancer treatment, health-related quality of life should also be considered during the period of anticancer treatment and best supportive care. Among male advanced cancer patients with cachexia, up to 70% of patients reportedly have hypogonadism defined as low serum testosterone levels which could induce many cancer-related symptoms including cachexia itself (1, 2, 6). Testosterone functions to keep males healthy and decreases gradually with age (7, 8). Testosterone increases bone mineral density and muscle mass (9, 10), improves mental function and cognitive impairment (11, 12), decrease lower urinary tract symptoms and nocturia (13, 14), and maintains cardiovascular health (15). On the other hand, androgen receptors in

prostate cancer cells are important drivers of cancer progression and testosterone may be associated with carcinogenesis of prostate cancer and deteriorate benign prostate hyperplasia (16-18).

Although androgen replacement therapy reportedly improves symptoms caused by hypogonadism in non-cancer male patients, there are few studies showing the efficacy of androgen replacement therapy on symptoms in male advanced cancer patients (19). There have been no prospective studies comparing continuous testosterone administration to non-administration conducted to date. The ARTFORM study is the first study of its kind, and the efficacy of androgen replacement therapy is prospectively assessed from a patient perspective of direct clinical benefit using health-related quality of life questionnaires comparing testosterone administration patients to non-administration patients. The study will clarify the role of testosterone in male advanced cancer patients and the efficacy of androgen replacement therapy on cancer-related symptoms.

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None

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